18. (twice amended) The conjugate of claim 16 wherein the nucleic acid molecule is selected from the group consisting of triplex forming oligonucleotides, ribozymes, guide sequences for ribozymes, and antisense [in combination with means for delivering the nucleic acid molecule directly to the endothelium of large vessels].

19. (twice amended) The conjugate of claim 13 wherein the molecule to be delivered is a non-nucleic acid drug.

Remarks

Rejections under 35 U.S.C. §112, first paragraph

Claims 5-7 and 16-19 were rejected under 35 U.S.C. §112, as non-enabled by the specification for *in vivo* delivery of genes to cells. This rejection is traversed if applied to the amended claims.

Solely to facilitate prosecution, the claims have been amended to recite that the EPCR is bound to the cells *in vitro*, by direct contact using a catheter or during a surgical procedure in which the conjugate is directly applied to the endothelial cells to be treated (which is clearly no less enabled or more difficult or less predictable than the in vitro studies described in detail in the application, and for which the examiner has provided absolutely no evidence would not be predictable and successful). Support for this amendment is found in the application at page 10, lines 1-4, and 15-27. The examiner's attention is drawn in particular to the references cited therein, which demonstrate that direct application of genes to cells using the cited procedures and materials were effective in introducing the nucleic acid molecules to be delivered to the cells.

Copies of abstracts of work done in the same time period as when this application was filed are enclosed to demonstrate that those skilled in the art of gene delivery were able to transfer genes as claimed, although different delivery systems. No evidence has been provided

which demonstrates that the claimed conjugates would not be equally effective. Indeed, since soluble EPCR (although not a conjugate) circulates in the body and binds to endothelial cells, there is even more evidence that in the case using an EPCR-binding conjugate one would expect success. These abstracts are Nikol, et al., "Needle injection catheter delivery of the genes for an antibacterial agent inhibits neointimal formation" Gene Ther. 6(5):737-748 (May 1999), Alexander, et al., "Gene transfer and models of gene therapy for the myocardium" Clin. Exp. Pharmacol. Physiol. 26(():661-668 (1999), and Wivel, et al., "Methods of gene delivery" Hematol. Oncol. Clin. North. Am. 12(3):483-501 (1998).

The claims have also been amended to refer to endothelial cells rather than endothelium. claim 1 has also been amended to delete the objected to language "where they are active".

Rejections under 35 U.S.C. §102(b)

Claims 13, 15, 20 and 22 were rejected under 35 U.S.C. §102(e) as disclosed by U.S. patent No. 5,847,085 to Esmon. This rejection is respectfully traversed.

Claims 13, 15, 20 and 22 are all directed to a conjugate. The claim requires the following two elements:

(1) an agent binding selectively to endothelial protein C receptor (EPCR) selected from the group consisting of protein C, activated protein C, antibodies reactive with EPCR and fragments thereof binding to EPCR, and

(2) a molecule to be delivered to a large vessel endothelial cell, wherein the molecule is not a diagnostic label.

The '085 patent does not disclose a conjugate. The patent describes a protein C molecule (which does meet with the definition of element 1) but no molecule bound thereto to be delivered. The patent is instead drawn to a modified protein C in which a region *of the protein C*

molecule per se is substituted with the equivalent region of prothrombin, thereby altering the properties of the protein C molecule.

Allowance of claims 1-25, as amended, is earnestly solicited. All claims as pending upon entry of this amendment are attached in an appendix to facilitate review by the examiner.

Respectfully submitted,

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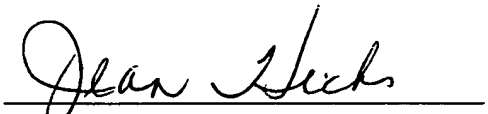
Certificate of Mailing under 37 C.F.R. § 1.8(a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: December 7, 2000



Jean Hicks